Lithium: past, present and future.

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Treatment guidelines recommend lithium as a first-line option for relapse prevention and suicide prevention in bipolar-I-disorder. However, there is a disparity between research efficacy and clinical effectiveness, with only a third of patients having an excellent response to long-term treatment.[1] Today, lithium use is in decline[2] – the predominance of sub-optimal responses, the need for blood monitoring, the perception that lithium is more toxic than other medications and the often-lengthy trials necessary to determine response likely all contribute. For every factor, there is scope to improve our knowledge of lithium and room to move towards more effective, safe and ultimately personalised prescription. Such is the goal of the R-LiNK consortium (Response to Lithium Network; www.r-link.eu.com), but before considering this, we reflect on the history of lithium in this year of anniversaries.[3]

In 1843, the aptly named Alexander Ure suggested lithium carbonate might treat urinary calculi but it was Garrod who first described its use 160 years ago (in gout and related brain maladies). 125 years ago, the Lange brothers reported on the use of lithium salts in periodical depression and Annie 'Londonderry' became the first female round-the-world cyclist, sponsored by the 'lithia water' company whose name she briefly adopted. Lithium salts were subsequently added to tonics (notably 7-UP, launched 90 years ago as 'bib-labelled lithiated lemon-lime soda') and advocated as table salt substitutes for those with cardiac disease taking low sodium diets. The latter proved toxic and it was withdrawn from the US market in 1949.[4] The same year, seventy years ago this month, also saw the publication of John Cade's seminal paper describing its use in the treatment of mania.[5]

Efficacy in mania was soon confirmed but perhaps the most important effect of lithium – the prevention of recurrence in bipolar disorder – was not a simple thing to establish.[6] Even the notion of prophylaxis in psychiatry was contested and 50 years ago, debate raged (not least in The Lancet).[7] Lithium was variously cast as panacea, placebo or poison. Technological advances in serum monitoring permitted the widespread clinical use of lithium but it was the development of novel trial methodology that provided the empirical evidence necessary

to overcome the scepticism surrounding relapse prevention.[3,6] Essentially, lithium did not benefit all, but proved remarkably effective for some.

Response to lithium is an obvious stratification point. A predictor, discernable early in prophylaxis, could avoid the need for lengthy treatment trials and target lithium to those most likely to benefit. Regrettably, despite significant research effort, individual clinical markers and isolated biological markers inadequately inform practice due to low specificity, sensitivity and predictive power.[1] An integrated science approach combining clinical and multimodal biomarkers may fare better. The ambition of R-LiNK is to determine which patients with bipolar disorder are most eligible for long-term lithium treatment in terms of response, safety and tolerability. We have established a large expert multidisciplinary European network with shared protocols and harmonised research procedures, supported by an international advisory committee. Here we share some innovations in our inaugural project, funded by the European Union Horizon 2020 program.

In 16 centres, over 300 individuals will be enrolled in a prospective two-year cohort study of lithium in bipolar-I-disorder. In this representative sample, treatment decisions will remain rooted in clinical practice to enhance transferability of results. Brain imaging, blood molecular and metabolic biomarkers acquired before and 12 weeks after lithium initiation will capture intra-individual biological changes for testing with respect to long-term response. Monthly assessment during the follow-up period will allow precise evaluations of response and tolerance (such as ecological digital phenotypes, clinical symptoms, illness activity and adverse events) as well as treatment adherence (to avoid misclassification in response status). At conclusion, a consensus panel approach will classify individuals to a response category.

We will test the predictive potential of clinical characteristics, digital phenotypes, omics and neuroimaging parameters as biomarkers and combined biosignatures, primarily against categorical response. More innovatively, we will assess response dimensionally, exploring

the pace and pattern of change in a mirror image analysis, as well as its relationship to non-response, non-adherence and poor tolerability. The study also embeds a health economic analysis.

As an example of preparations, we have harmonised MRI sequences (structural, diffusion-weighted and proton spectroscopy) across the different centres and scanners, with secure double-pseudomised data export systems embedding quality control measures. Novel to R-LiNK, six centres have been equipped for ^{7}Li-MRI, a new technique that directly measures brain lithium distribution,[8] the heterogeneity of which may be related to therapeutic response and tolerance. Further, we have successfully combined ^{7}Li-MRI with MRI measures of lithium's tissue-level effects,[9] including those with the potential to predict response.[10]

Using machine-learning to combine clinical and multimodal biosignatures, we anticipate a 'prediction algorithm' capable of guiding early treatment decisions (first three months) and avoiding the need for patients to submit to lengthy trials of lithium. We believe that the dissemination and application of harmonised methods will prove central to the development of personalised treatment in psychiatry, particularly for the validation studies envisaged.

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Author contributions

Cousins DA performed a literature search and prepared the first and final drafts. All other authors contributed to the writing and critical review of the document, and approved the final version.

Declaration of interests

Cousins DA declares honoraria from Lundbeck for lectures. He is co-investigator for the BRIGhTMIND study (EME National Institute for Health Research). He declares no shareholdings in pharmaceutical companies.

Squarcina L and Boumezbeur F declare no conflicts of interest.

Young AH declares paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: AstraZenaca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma. He is a paid consultant Johnson & Johnson and Livanova, and has received honoraria for attending advisory boards and presenting talks at meetings organised by LivaNova. He is the Principal Investigator for: Restore-Life VNS registry study funded by LivaNova; ESKETINTRD3004 (An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression) sponsored by Janssen-Cilag; The Effects of Psilocybin on Cognitive Function in Healthy Participants; The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD). Past and present grant funding received from NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK); Janssen (UK). He declares no shareholdings in pharmaceutical companies.

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